to be active) to produce liver cancer. It is likely that these chemicals bind through reversible hydrophobic and electrostatic interactions to proteins. The trihalomethanes can act directly at very high doses to produce anesthesia. However, their more severe toxicities are produced by being metabolized oxidatively to phosgene, reductively to a free radical, or reacting with glutathione to produce a third reactive intermediate. These reactive intermediates interact covalently with proteins and nucleic acids to produce toxicity and induce mutation, respectively. Oxidants can also produce damage by inducing oxidative stress. Generation of hydrogen peroxide, superoxide radical, and hydroxyl radical can produce damage to cell membranes and produce oxidative damage to purine and pyrmidine bases in DNA *in vivo*. Such reactions may occur spontaneously, but in some cases various enzymes that are present in the body accelerate them.

Impact of Bromine Substitution on Metabolism Leading to Reactive Intermediates. Halogen substitution on organic molecules provides an electronegative point of attack for either oxidative or reductive metabolism. In reductive dehalogenation reactions, free radicals are generated that lead to oxidative stress or to direct damage by the halogen radical. As halogens become larger, they become more electronegative and are more easily removed. Chlorine is a better leaving group than fluorine and bromine is better than chlorine. Therefore, toxicities that are the result of interactions of reactive metabolites are generally greater if bromine is substituted on a carbon instead of chlorine. To the extent that these metabolites can reach the DNA in the cell, they are frequently mutagenic.

The limited comparisons of toxic and carcinogenic effects of the relatively small numbers of brominated disinfection by-products are consistent with this hypothesis. The weight of evidence (induction of tumors in multiple species, multiple sites, and sites of relatively low incidence) of bromodichloromethane is much stronger than for chloroform. Moreover, the carcinogenic potency of bromodichloromethane is approximately 10-times that of chloroform using the linearized multistage model for comparisons at low doses (Bull and Kopfler, 1991).

Mutagenicity as a Major Determinant for Using Linear Approaches to Low-dose Extrapolation. The mutagenic activity of a chemical is a major determinant of whether linear methods are to be used for low dose extrapolation (USEPA, 1996). Within the THM and haloacetic acid groups of DBPs that have been investigated, the chlorinated members of the group are very inconsistently active in mutagenesis assays. There are three different pathways

for metabolizing the THMs to reactive metabolites. In the two of the three pathways that have been investigated, substitution of bromine increases the mutagenic activity significantly above that seen with the chlorinated analogs (Zieger, 1990; Pegram et al., 1997). Dichloroacetic acid and trichloroacetic acid are very weak mutagens, requiring greater than millimolar concentrations to product modest responses (Harrington-Brock et al., 1998; Giller et al., 1997). Dibromoacetic acid and tribromoacetic acid are at least an order of magnitude more potent as mutagens in the Salmonella fluctuation assay (Giller et al., 1997).

Mutagenic activity of a compound assumes this importance based on the assumption that mutagenic events are cumulative with dose. Mutations are essentially irreversible events to the extent that the mutated cell and its progeny survive.

Based on the relative lack of data implicating a mutagenic mechanism for chloroform, an MCLG (maximum contaminant level goal) of 300 μg/L was recommended by the USEPA in a Notice of Data Availability (USEPA, 1998b). However, it is highly improbable that bromodichloromethane would be treated in the same way. In all probability, an MCLG = 0 will be maintained for bromodichloromethane because of its mutagenic activity and because of its more robust activity as a carcinogen. It is also improbable that dichloroacetic acid and trichloroacetic acid will be treated with linear-low dose extrapolation. As with bromodichloromethane, the mutagenic activity associated with the brominated haloacetic acids may also be used to rationalize linear low-dose extrapolation for these chemicals. In addition, the brominated haloacetic acids have been shown to produce a sustained elevation of oxidatively damaged DNA in the liver of chronically treated mice (Parrish et al., 1996), an effect not observed with dichloroacetic acid and trichloroacetic acid. As a result, the MCLGs proposed for the chlorinated vs. the brominated haloacetic acids could vary widely even though they have approximately the same carcinogenic potency in animal studies (Bull, unpublished data).

3.2.2 Bromate

When ozone is used in the disinfection of water containing significant amounts of bromide, the formation of bromate will result. When the concentrations of bromate produced in these circumstances are compared to those which induce cancer in rats (Kurokawa et al., 1986), the margin of safety is significantly lower than for disinfectant by-products that are produced with chlorination.

Estimated Cancer Risk. Applying the linearized multistage model to data obtained in cancer bioassays in rats, the concentrations of bromate associated with the 1 in a million additional lifetime risk is 0.05 μg/L (Bull and Kopfler, 1991). The 1 in 10,000 added risk is estimated at 5 μg/L which approximates the practical quantitation limit (PQL) in water.

Lack of Toxicokinetic and Toxicodynamic Data. The risk that bromate represents as a cancer hazard in humans may not be accurately reflected by the linearized multistage model. Unlike chlorination, no epidemiological studies have been conducted to suggest that ozonation of water carries a cancer risk for humans. Available data, however, suggest a relationship with oxidative damage to DNA in the induction of renal tumors (Umemura et al., 1993). The actual mechanisms involved are somewhat controversial. *In vitro* studies of bromate-induced DNA damage suggest that the process requires glutathione and produces a damage more consistent with the generation of bromide radicals than reactive oxygen species (Ballmaier and Epe, 1995). Conversely, Chipman et al., (1998) found little dependence upon glutathione *in vivo*, but indirect methods (i.e. glutathione depletion) were used to investigate glutathione dependence. On the other hand, these investigators did find evidence of lipid peroxidation in the kidney of rats following 100 mg/kg dose of potassium bromate, but not at 20 mg/kg. Neither case provided a rationale for why these effects were observed in the kidney and not other organs like the liver (Cho et al., 1993; Lee et al., 1996). The oxidative damage to DNA is also produced at very high rates by the normal energy metabolism of the body. The repair mechanisms for this type of damage are very rapid and efficient (Lee et al., 1996). At low doses, the amount of oxidative damage anticipated from bromate would be very small compared to the damage induced by normal metabolism. Consequently, it is likely that cancer risk would be low at the concentrations of bromate that might be anticipated in ozonated drinking water. Irrespective of a detailed mechanism, however, it will be necessary to obtain a much clearer and quantitative model of the toxicokinetics and toxicodynamic nature of bromate-induced cancer. The research of Lee et al. (1996) provides an excellent start by identifying a critical biomarker for kidney cancer, but has yet to be coupled with biological responses in a quantitative way. Thus, detailed toxicokinetic and toxicodynamic data appear necessary to provide evidence that non-linear extrapolation is appropriate for bromate-induced cancer.

3.3 Variations in sensitivity in the human population.

It is important to acknowledge that the differences in epidemiological and toxicological studies of disinfection by-products could be that rodents are a poor representation of the distribution of human sensitivities to toxic chemicals. In general rodents used in toxicological tests are inbred strains. Frequently, these strains are chosen because they are sensitive models for certain types of toxic effects. While this may be generally true, it does not always hold true in particular cases. The factors that influence sensitivities to toxic chemicals frequently have a very specific basis that is not necessarily reflected by so-called "sensitive experimental animal models". It is beyond the scope of this report to cover this subject in a comprehensive way. However, there are two types of interaction that need to be identified and discussed in an illustrative way. Once the mechanisms involved in these two general processes are identified, the identification of traits that characterize sensitive populations can be done rationally in a chemical-specific way.

3.3.1 Enzymes involved in metabolism of disinfection by-products.

Several types of metabolic processes are involved in the toxicology of disinfection by-products. However, a broad class of enzymes, glutathione-S-transferases, have been implicated in the toxicities of the trihalomethanes, the haloacetic acids, and the haloacetonitriles. In the case of the THMs, the theta isoform appears to be capable of producing a mutagenic metabolite (Pegram et al., 1997). This isoform is not expressed by approximately 40% of the U.S. population. Therefore, the sensitive population may be only 60% of the human population. Conversely, evidence has been gathered that demonstrates that a new glutathione-S-transferase, the zeta isoform, acts to detoxify dichloroacetic acid (Tong and Anders, 1998). If there is a significant fraction of the population that did not express this enzyme, that fraction of the population could be extremely sensitive to this disinfection by-product.

3.3.2 Susceptibility to effects of DBPs.

Other host-related factors that could be the basis for higher sensitivity of humans to disinfection by-products are more difficult to identify, but may be more important than variations in enzymes involved in the metabolism of DBPs. Broad examples can be provided, however. If a disinfection by-product acts through damaging DNA, lack of the enzymes that recognize and

repair those lesions could make an individual much more sensitive. Some disinfection by-products (e.g. the haloacetic acids) appear to act by interfering with cellular signaling systems that are activated by insulin and related growth factors. Diabetics are much more prone to the development of liver cancer than the rest of the population. Consequently, if epidemiological studies had focused on this subpopulation, a risk of liver cancer may have been identified.

3.4 Summary

From the health effects standpoint, there are issues that surround bromide and brominated by-products that can be resolved in the next 5-10 years, but others that will require decades to solve. Properly directed toxicological screening studies and mechanistic studies could provide much better perspective on the actual risks associated with disinfection by-products in the shorter time frame. Without specific and detailed knowledge of the mechanisms by which disinfection by-product toxicity is induced, it is very difficult to identify those variables that would affect the distribution of human sensitivities to these chemicals that could be applied in a meaningful way in epidemiological studies.

The importance of establishing the mode of action by which chemicals induce toxicity, particularly in carcinogenesis, cannot be overstated. Nowhere is this more apparent than when considering the potential differences in risk that may exist between chlorinated and brominated by-products. Clearly, these molecules will share some aspect of their mechanism of action. As bromine substitution increases, however, multiple mechanisms are likely to become apparent. The non-genotoxic mechanism found with the corresponding chlorinated DBP will undoubtedly still be represented, but the brominated analogs are significantly more likely to add mechanisms of carcinogenesis involving mutagenesis. Thus, not only will the mechanisms contributing to the adverse response become more diverse, but they will also require linear extrapolation. In some cases, the mechanism responsible for the effect induced by the chlorinated analogs may actually disappear as the degree of bromine substitution increases. The permission from one mechanism to another could lead to some complex structure-activity relationships that might have to be resolved before the relative impact at concentrations found in drinking water can be estimated with confidence.

4.0 Regulatory Background

The purpose of this section is to provide a perspective on possible regulatory criteria that may influence treatment and associated cost impacts on public drinking water drinking systems using the Bay-Delta as their source water.

4.1 Overview of 1996 SDWA Amendments as they Pertain to DBPs/Microbes

In 1996, Congress issued amendments to the Safe Drinking Water Act requiring EPA to develop regulations within a specified time. These include promulgation of the Interim Enhanced Surface Water Treatment Rule (IESWTR) and Stage 1 Disinfectants and Disinfection By-Products Rule (DBPR1) by November 1998, a Long Term Enhanced Surface Water Treatment Rule (LT1ESWTR) by November 2000, and a Stage 2 Disinfectants and Disinfection By-Products Rule (DBPR2) by May 2002. As part of the 1996 amendments, Congress also requires EPA to consider risk from contaminants that might be indirectly affected by regulation. In this regard, EPA intends to propose and promulgate a Long Term 2 Enhanced Surface Water Treatment Rule (LT2ESWTR) concurrently with the DBPR2.

4.2 Overview of DBPR1/IESWTR/LT1ESWTR

The purpose of the DBPR1 is to reduce risks from disinfectants and DBPs in public water systems which disinfect. Unlike the Maximum Contaminant Level (MCL) of 100 ug/l for total trihalomethanes (TTHMs), which only pertains to systems serving 10,000 people or more, the DBPR1 will apply to all system sizes. The purpose of the IESWTR is to reduce risks from pathogens, especially *Cryptosporidium*, and to prevent increases in microbial risk while systems comply with the DBPR1. With the exception of sanitary survey requirements (which will pertain to all system sizes), the IESWTR will pertain to systems serving 10,000 or more people. In November 1997, EPA issued two Notices of Data Availability in the Federal Register indicating the rationale supporting the criteria intended for promulgation in the DBPR1 and the IESWTR.

Criteria under consideration for the final DBPR1 include: (i) MCLs for TTHMs (0.080 mg/L = 80 ug/L), the sum total of 5 haloacetic acid concentrations otherwise known as HAA_5 (0.060 mg/L = 60 ug/L), bromate/BrO_3^- (0.01 mg/L = 10 ug/L), and chlorite/ClO_2^- (1.0 mg/L = 1,000 ug/L); (ii) maximum residual disinfectant levels for chlorine (4.0 mg/L), chloramines (4.0 mg/L), and chlorine dioxide (0.8 mg/L); and (iii) enhanced coagulation requirements for systems

using conventional treatment or softening to remove DBP precursors (measured as percent reductions of total organic carbon (TOC)).

Criteria under consideration for the final IESWTR include: (i) tightening the combined filter turbidity performance criteria for systems using rapid sand filtration to less than 0.3 NTU in at least 95% of turbidity measurements taken each month; (ii) continuous turbidity monitoring requirements for individual filters and reporting of results to States depending upon individual filter performance; (iii) a provision that would not allow systems to lower existing levels of inactivation to comply with the Stage 1 DBPR MCLs without first consulting with the responsible State officials; and (iv) provisions that would require the responsible State agencies to conduct sanitary surveys of all surface water systems (including those serving <10,000 persons), and for systems to implement remedial action if problems are identified by State agencies. A sanitary survey incorporates not only an inspection of the treatment plant, but examination of a wider range of factors that influence the quality of drinking water, including the watershed and the distribution and storage system.

EPA envisions similar requirements to the IESWTR being issued for systems serving fewer than 10,000 persons in the LT1ESWTR scheduled for proposal in November 1999, and for promulgation in November 2000.

EPA intends to set compliance dates for the DBPR1 that will coincide with compliance dates for the IESWTR (November 2001 for systems serving 10,000 or more people) and the LT1ESWTR (November 2003 for systems serving less than 10,000 people).

EPA is planning to conduct stakeholder meetings beginning in December 1998 to discuss information and the process to support the development of the DBPR2 and LT2ESWTR. Major issues related to these rules are discussed below.

4.3 DBPR2 Issues

Major issues with developing the DBPR2 include: interpretation of cancer, developmental, and reproductive risk associated with DBPs from limited toxicological and epidemiological data; assessing the feasibility and costs of using various treatment technologies to reduce DBP concentration levels; and assessing the potential changes in microbial risk that might result from treatment changes to control for DBPs. Addressing the above issues will help determine the extent to which additional regulation may be appropriate such as whether to set

MCLs for DBP groups, individual DBPs, or treatment technique requirements (e.g., limits for total organic halides (TOX), or TOC removal requirements). Another issue may be whether MCLs should be set based on a running annual average as is currently the case, or on maximum single event concentration levels. MCLs based on maximum values within a distribution system would prevent all people from being exposed above a certain level. Such a strategy could become important if developmental or reproductive effects from exposure to DBPs are determined to be of concern.

Several specific issues relative to the broad generic issues discussed above may have particular significance for utilities using the Bay Delta as their source water. These include: (i) the risk associated with brominated DBP species versus the risks from the complete mixture of chlorinated DBPs; and (ii) if the risks from brominated species are deemed substantially more significant than those from the chlorinated species, the extent to which brominated species formed primarily through chlorination (e.g., bromodichloromethane or bromochloroacetic acid) or ozonation (e.g., bromate) can be controlled.

The setting of any new MCLs or treatment technique requirements will consider potential exposures (and associated risks) able to be avoided, and the technical feasibility and costs for reducing exposures on a national level. In considering this type of analysis, it becomes important to understand the national distribution of source water quality parameters (e.g., bromide, TOC, UVA_{254}) that most significantly affect the treatability of the water. Systems using the Bay-Delta as their source water (primarily because of the high bromide content), may have greater difficulty than the average utility in the U.S. in meeting a particular regulatory endpoint; another important consideration is the character of the TOC in Bay-Delta water. This regional consideration is also relevant to the national standard-setting provision that treatment must be affordable for large systems. The significance of this issue may also be largely influenced by the co-occurrence of pathogens (particularly *Cryptosporidium*) and DBP precursors. Depending upon the requirements of the LT2ESWTR, the level of inactivation required to control microbial risks could make it more difficult for systems to comply with the DBPR2 criteria. For example, a system with high levels of *Cryptosporidium* and DBP precursors (bromide and TOC) in their source water may have greater difficulty in complying with the DBPR2 and LT2ESWTR than systems with average source water quality. Each rule will have to consider and appropriately

address the factors of affordability and availability of treatment raised by compliance with the other rule.

4.4 LT2ESWTR Issues

Major issues with developing the LT2ESWTR include: estimating the microbial risk likely to remain after implementation of the IESWTR and LT1ESWTR, given limitations of data; determining appropriate risk goals (e.g., EPA's 1994 proposed 10^{-4} annual risk goal for *Giardia* or *Cryposporidium*); and determining the appropriate regulatory framework and target organism(s). Several regulatory frameworks were considered under the 1994 proposed IESWTR and are likely to be revisited under the development of the LT2ESWTR. These include: a proportional treatment requirement, (where systems might be required to achieve at all times a minimum level of total removal/inactivation for *Cryptosporidium*, depending upon an estimated reasonable worst case pathogen occurrence in the source water); and a fixed level treatment requirement (where all systems would be required to achieve at least the same minimum level of treatment, with exceptions allowed, depending upon site specific characteristics).

Major constraints with developing the IESWTR included: lack of available methods for adequately measuring *Giardia* or *Cryptosporidium* in the source water, and limitations by which treatment efficiencies (physical removal and chemical inactivation) for these organisms could be practically determined. The extent to which these issues can be resolved may largely influence criteria to be included in the LT2ESWTR.

Although LT2ESWTR criteria will not become apparent for quite some time, factors which could significantly influence the impact of this rule on a particular utility include the magnitude and variability of *Cryptosporidium* in the source water, physical removal efficiencies for *Cryptosporidium*, and the feasibility of inactivating *Cryptosporidium* while also meeting new regulations for DBPs (as discussed above under DBPR2 issues). Systems with low pathogen loadings in their source water and/or high physical removal efficiencies are likely to be less affected by any inactivation requirements that might be specified for *Cryptosporidium*.

4.5 Recommendation

The CALFED program should strive to deliver the highest possible raw-water quality to the sources used for drinking water supply. This effort will minimize treatment costs and the threat to public health from drinking water.

5.0 Treatment Considerations

5.1 Overview of Treatment Considerations

A variety of treatment technologies are available for the disinfection of water. A number of these (e.g. chlorination, ozonation) produce potentially harmful disinfection by-products (e.g. trihalomethanes, haloacetic acids, bromate). The incorporation of bromine into these disinfection by-products increases as the bromide concentration in the water being treated increases. For example, the speciation of THMs shifts away from chloroform and toward bromodichloromethane, dibromochloromethane, and bromoform, respectively, as the concentration of bromide increases. Likewise, the speciation of haloacetic acids shifts away from di- and trichloroacetic acid towards bromochloroacetic acid and bromodichloroacetic acid, respectively, with increasing bromide concentrations. In the case of ozonation, bromate formation increases with increasing bromide concentrations. If disinfection requirements become more stringent with future regulations, greater concentrations of disinfectants may need to be applied, resulting in greater concentrations of disinfection by-products unless there is a shift toward higher quality source water or greater degrees of pretreatment prior to disinfection.

To control the formation of these potentially harmful disinfection by-products, several treatment strategies can be employed:

(a) removal of the organic precursors with which the disinfectant reacts prior to the application of the disinfectant;
(b) removal of the bromide prior to disinfection;
(c) removal of the disinfection by-products after they are formed;
(d) modification of treatment conditions to limit the formation of specific DBPs; or
(e) use of alternative disinfectants which do not produce DBPs of health concern.